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TOPIC HIGHLIGHT

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Modification in the diet can induce beneficial effects against breast cancer

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Abstract

The population tends to consume foods that in addition to their nutritional values can offer some benefits to their health. There are many epidemiological evidences and research studies in animal models suggesting that diet plays an important role in breast cancer prevention or progression. This review summarized some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing lactic acid bacteria in cancer prevention and/or treatment was especially discussed. It was observed that a balance of fatty acids similar to those of traditional Mediterranean diet, the consumption of fruits and vegetables, dietary fiber intake, vitamin supplementation are, along with the intake of probiotic products, the most extensively studied by the negative association to breast cancer risk. The consumption of probiotics and fermented products containing lactic acid bacteria was associated to reduce breast cancer risk in some epidemiological studies. The use of animal models showed the modulation of the host's immune response as one of the important effects associated to the benefices observed with most probiotics. However; future assays in human are very important before the medical community can accept the addition of probiotic or fermented milks containing lactic acid bacteria as supplements for cancer patients.

Key words: Breast cancer; Nutrition; Probiotic; Fermented products

Core tip: The population tends to consume foods that in addition to their nutritional values can offer some benefits to their health. In this sense, there are many epidemiological evidences and research studies suggesting that diet plays an important role in breast cancer prevention or progression. This review summarized some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing lactic acid bacteria in cancer prevention and / or treatment was especially discussed.

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INTRODUCTION

The population tends to consume foods that in addition

to their nutritional values can offer some benefits to their health.

The WHO reported that approximately 30% of cancer deaths are due to five behavioral risk factors and diet, such as high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use[1]

Breast cancer is a type of tumour in which there are many reports about the influence of nutrition[2,3].

Lactic acid bacteria (LAB) represent a heterogeneous group of microorganisms that are present in the normal diet of many people and also in the gastrointestinal and urogenital tract of animals, and some of these claimed to be probiotics. Probiotics are defined as live microorganisms which when administered in adequate amounts, confer a health benefit on the host[4]. These microorganisms and fermented foods containing LAB were growing in their popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers[5,6].

The use of experimental animal models has a number of advantages in that the environmental conditions and genetics can be either controlled or defined. The value of the models is the insight they can provide into the complex, multi-faceted processes and mechanisms that can result in cancer development. *In vitro* assays are also important to understand the mechanisms of action involved in the LAB or other dietary effects. However, the application of dietary modifications against cancer needs to be ultimately tested in human trials.

This review summarizes some of the relevant researches about nutrition and cancer during the last years, especially in breast cancer. The analysis of probiotics and fermented products containing LAB in cancer prevention and / or treatment will be discussed separately, with emphasis in the possible mechanisms involved.

NUTRITION AND CANCER

Several studies have been demonstrated a relationship (either beneficial or harmful) between diet and development of different types of cancer[7-9]. High fat diet, fiber consumption and vitamins are among dietary habits more reported by their association with cancer along with probiotic supplements, that will be discussed in a separately section.

Calorie restriction without malnutrition was associated to cancer prevention[10]. This effect was related to the reduction in the activity of pro-aging pathways, inflammation in the pre-cancerous cells, and to the increase in the apoptosis of damaged cells.

Several epidemiological studies have been shown the relationship between increase consumption of high fat diet and the risk to develop cancer, such as kidney, stomach, lung, esophagus, colon and breast cancer. Colorectal cancer (CRC) is a tumour for which there are many studies that associate obesity with increased risk, especially in men[11]. The exact mechanisms of this relationship are still unknown, but metabolic syndrome, insulin resistance[12], modifications in levels of adipocytokines[13] seem to be implicated. The role of the microbiota in the maintenance of intestinal homeostasis, and it relationship with intestinal inflammation and colon carcinogenesis was also extensively studied[14-16].

Dietary fat intake was also related to risk of ovarian cancer. It was suggested that higher intake of omega-3 may be protective, whereas high consumption of trans fat may increase risk of this cancer[17].

The fiber consumption is another important component of the diet that was associated inversely with cancer risk, such as CRC[18], nasopharyngeal carcinoma[19], oesophageal cancer[20].

The consumption of vitamins and mineral supplements are commonly used to prevent chronic diseases such as cancer. It was demonstrated that vitamin C (ascorbate) was selectively toxic to some types of tumor cells[21]. Recently, it was reported a case in which the consumption of this vitamin decreased chemotherapy associated side effects[22]. As regard to vitamin D, Bikle[23] revised its relationship with different cancers and described that animal and cellular studies supported a role for vitamin D in the prevention and treatment of cancer, but the same conclusion was not arrived from clinical studies.

Folate is essential for DNA synthesis and methylation and its role against cancer is controversial, even against one type of cancer, such as for prostate cancer[24]. Some studies implicated folates with tumour progression, such as the work reported by Dixon *et al*[25] showing evidences that folate intake affects ovarian cancer survival. On other hand, the chemopreventive effect of folic acid was evaluated *in vivo* using rat as model for liver carcinogenesis. This effect was observed in association with tributyrin and was related to the potential to inhibit tumour angiogenesis[26]. A recent review and meta-analysis showed that dietary folate intake was associated with a decreased risk of esophageal and pancreatic cancer, but not gastric cancer[27].

NUTRTION AND BREAST CANCER

There are many epidemiological evidences and research studies in human and animals suggesting that diet plays an important role in breast cancer prevention or progression[2,3]. Diet represents one of the most modifiable risk factors for breast cancer[28]. Changes in the dietary patterns are not only related to less risk but also patients diagnosed and treated for breast cancer who pursue healthier dietary habits can improve their health and survival.

The relationship between obesity and breast cancer was reviewed in many articles because the high incidence and prevalence of both diseases. Overweight and obesity at the time of diagnosis were associated with a worse prognosis in breast cancer patients[29]. A study in Italy showed that a diet high in glycemic load was associated with increased breast cancer risk[30].

A systematic review showed that there are some strat-

egies to prevent weight gain that may decrease the risk of breast cancer or improve cancer outcomes in women with breast cancer[31].

de Lorgeril and Salen suggested that a high omega-3 to omega-6 ratio, such as the case of traditional Mediterranean diet, reduce the risk of cancer, especially breast cancer[32]. A cohort study of breast cancer survivors showed that intake of marine fatty acids EPA (eicosapentaenoic) plus DHA (Docosahexaenoic) was associated with improved prognosis[33]. Omega-3 fatty acid, in particular EPA and DHA found principally in oily fish have been demonstrated to exert anti-angiogenic effects inhibiting production of different angiogenic mediators[34]. The beneficial effect of EPA and DHA intakes was also associated by reducing inflammation through different mechanisms such as the suppression of NF-κB, and the alteration of the plasma membrane micro-organization (lipid rafts)[35].

Canola oil has also been associated with a reduced risk of breast cancer. The inhibition of cancer cells *in vitro* and the reduction of tumour volume in rats with chemical induced mammary tumour that consumed canola oil was reported[36]. It was also suggested that canola oil can be used as prenatal nutritional strategies to reduce breast cancer risk in humans[37]. This suggestion was based in results obtained *in vivo* using a chemical induced mammary tumour in offspring rats of canola-fed dams. These animals showed significantly decreased tumor volume with increased survival rate comparing to the control group whose mothers received control diet with soybean oil during pregnancy and lactation.

Diets rich in fruits and vegetables are also implicated in breast cancer risk reduction. A meta-analysis including fifteen prospective studies that reported decreased risk of breast cancer associated with fruit and vegetable intake, showed that high intake of fruits, and fruits and vegetables combined can be associated with reduction in risk of breast cancer[38]. Similar results were obtained in a meta-analysis of prospective studies of blood concentrations of carotenoids and breast cancer risk[39]. Carotenoid concentrations in blood can be used as biomarkers of fruit and vegetable intake and in this sense; the authors showed that blood concentrations of carotenoids were strongly associated with reduced breast cancer risk. Recently, an inverse association between citrus fruits intake and the risk of breast cancer was suggested[40].

Dietary fiber intake was also inversely associated with breast cancer risk[41]. The ingestion of dietary phytoestrogens may increase risk of estrogen receptor alpha (ERα)-positive breast cancer and this effect was associated with their estrogenic effects observed *in vitro* and *in vivo*. The proliferative effect of soy isoflavones was mainly observed in animal models of tumours. However; paradoxically, consumption of phytoestrogens has also been associated with reduced risk of breast cancer[42-46]. This controversy with regard to the effect of soy isoflavones on breast cancer risk was analyzed and it was demonstrated that soy isoflavone phase II metabolism differs between humans and rodents, and this should be taken in count to understand the value of the use of these rodents for investigate the effects of isoflavones in humans[47]. Epidemiologic data indicate that soy intake is associated with a decreased breast cancer risk in Asia. A systematic review among women showed the possible protective effect of isoflavones on breast cancer risk[48]. It was also demonstrated that soy isoflavone intake was associated with lower risk of recurrence among post-menopausal patients with breast cancer and those who were receiving adjuvant endocrine therapy[49].

The understandings of the hormonal and non-hormonal mechanisms by which isoflavones can exert the beneficial effects were subject of many researches. The chemical structure of soy isoflavones is similar to that of estrogens. They are therefore considered to be possible selective estrogen receptor modulators (SERMs), which may bind to estrogen receptors and selectively stimulate or inhibit estrogen-like action in various tissues[50]. It was demonstrated that sera of adult mice consuming soy isoflavone genistein (GEN) or blueberry (BB) polyphenol-containing diet altered mammosphere formation *in vitro* using receptor-positive and estrogen receptor-negative human breast cancer cell lines[51]. Recently, this group demonstrated that breast cancer prevention by GEN was related to the regulation of mammary adiposity[52]. The cytotoxic action of GEN against breast cancer cells involved mobilization of endogenous copper ions and generation of reactive oxygen species[53].

Vitamin supplementation is another strategy, as was explained above, used to reduce cancer risk. With regard breast cancer, there was no found clear evidence of cancer prevention for vitamin supplements[54]. Folates and folic acid were evaluated in breast cancer patients and also *in vivo* using animal models, and as was explained, the role of folates is controversial. There are epidemiological studies suggesting an inverse association between folate status and the risk of breast cancer[55,56]. Some studies have also suggested that with alcohol consumption, folate supplementation reduces the risk of breast cancer[57,58]. The beneficial effect associated to folate intake in some populations was associated to genetic polymorphisms of folate-metabolizing enzyme, methylenetetrahydrofolate reductase (MTHFR)[59]. A population-based case-control study in Saudi Arabia showed that the *MTHFR C677T* polymorphism may modify the association between dietary folate intake and breast cancer risk[60]. Similar results were obtained from the Shanghai Breast Cancer Study[61] and in a case-control study in the Jiangsu Province of China[62]. A recent work suggested that intake of natural folates can be inversely associated with breast cancer risk, but this association may vary by race, menopausal status or estrogen receptor status[63]. The authors also observed an increased risk in European American women with the highest intake of synthetic folate from fortified foods. In this sense, a systematic review analyzed the effect of high folate intake post fortification, especially when folic acid was used, and demonstrated a higher risk of breast can-

cer in these populations[64]. The authors showed the need to be cautious with high intakes of folic acid, especially in countries with mandatory food fortification, as Chile.

Animal models were used to understand the mechanisms by which folates and folic acid exert their effects, especially in breast cancer patients. Mammary tumors were chemically induced in rats and then, the animals received a diet containing different levels of folic acid[65]. Folic acid supplementation was associated with significantly higher volume of mammary tumors and increased expression of BAX, PARP, and HER.

Riboflavin intake was also analyzed and an inverse association with breast cancer risk was documented[66].

Selenium (Se) is an essential micronutrient having high anticancer properties in different animal models[67,68]. As regard to breast cancer, it was demonstrated, using an animal model, that organic Se supplementation may reduce breast cancer metastasis, while selenite exacerbated it[69].

Another dietary component (even though is minor in our diet) that was reported as effective against cancer is the inorganic sulfur. It was showed that inorganic sulfur significantly decreased proliferation of MDA-MB-231 human breast[70]. This effect was due to reduction of ErbB2 and ErbB3 protein and mRNA expression, affecting the he ErbB-Akt pathway. Previously, it was reported that inorganic sulfur reduced cancer cell motility and invasion by inhibiting activity and mRNA expression of matrix metalloproteases (MMP-2 and MMP-9)[71].

PROBIOTICS AND CANCER

Probiotic microorganisms and fermented foods containing LAB have been growing in popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers[5,6,72].

The effects of probiotics and fermented products on intestinal disorders have been the most extensively studied considering that these microorganisms enter the organism orally and can positively modulate the intestinal microbiota involved in many of these disorders. The benefits of probiotics on the gut immune system in the prevention of cancer has also been previously described[73,74]. There are many different mechanisms by which probiotics and fermented products containing viable LAB may lower the risk of colon cancer; among them, the modulation of the intestinal microbiota[75-80], the inactivation of carcinogenic compound[81-83], anti-oxidant effects[84-86], and the modulations of the host's immune response[87-89]. Recently, the administration of probiotic Dahi containing *Lactobacillus* (*L.*) *acidophilus* LaVK2 and *Bifidobacterium bifidum* BbVK3 alone or in combination of piroxicam showed anti-neoplastic and anti-proliferative activities in a model of DMH-induced CRC in rats[90].

It was also demonstrated that oral administration of probiotic microorganisms can influence mucosal sites different to the intestine due to the existence of the common mucosal immune system. In this sense, after intestinal stimulation, both B and T cells can migrate from Peyer's patches to mucosal membranes of the respiratory, gastrointestinal and genito-urinary tract, as well as to exocrine glands such as the lacrimal, salivary, mammary and prostatic glands[91]. The oral administration of *L. casei* CRL 431 to mice induced an immune stimulation not only at the intestinal level, but also in bronchus and mammary glands[92].

Beneficial effects of probiotic LAB administration were reported for non-intestinal tumors. The antitumor activity of *L. casei* CRL 431 was studied against a fibrosarcoma induced by methylcholantrene in mice. The administration of the probiotic strain inhibited tumor growth in a dose-dependent form[93,94], stimulated the immune system with high levels of macrophage activation (the main infiltrative cells in the tumor), high levels of TNFα and with a remarkable decrease in tumor volume.

The effect of LAB or fermented products containing these microorganisms in non-intestinal tumours reported during the last years (2011-2014) were obtained searching the words "probiotc and cancer" in PubMed database.

It was reported the beneficial effect against cervical cancer. A pilot study suggested that probiotic promotes the clearance of HPV-related cytological abnormalities[95]. Common vaginal lactobacilli exerted cytotoxic effects on cervical tumour cells independently of pH and lactate[96]. *L. casei* displaying E7 antigen at its surface protected mice against human papillomavirus type 16-induced tumours[97].

As regard hepatocarcinoma, the administration of probiotic fermented milk containing *L. rhamnosus* GG and, *L. casei* strain Shirota with chlorophyllin reduced liver pre-carcinogenic events in rat AFB1 induced liver carcinogenesis. This effect was attributed to an increased antioxidant status and decreased expression of oncogenes[98].

The beneficial effects of LAB were also reported in animal models of oral cancer[99], and skin carcinogenesis[100].

PROBIOTICS AND BREAST CANCER

Breast cancer is another tumour in which there are reports about the beneficial effects of probiotic administration. Many reports analyzed, as was explained above, the association of soy based products and especially soy isoflavones with breast cancer risk. In this context, soy isoflavone ingestion was studied accompanied with the co-administration of probiotic bacteria, and it was observed that high concentrations of probiotics may alter the metabolism of isoflavones[101]. Recently, the consumption of beverages containing *L. casei* Shirota and soy isoflavone was inversely associated with the incidence of breast cancer in Japanese women when they were consumed regularly since adolescence[102]. The cooperative prevention mechanism of soymilk and *L. casei* Shirota was evaluated

Table 1 Examples of breast cancer animal models that have demonstrated the beneficial effects of lactic acid bacteria

Model	Results	Mechanisms	LAB	Ref.
4T1 tumour bearing mice	Significant decrease of tumour growth	Modulation of the host's immune response	*L. acidophilus* isolated from traditional home-made yogurt and from neonatal stool	[113]
Mice bearing invasive ductal carcinoma	Decrease of tumour growth rate and prolongation of mice survival	Modulation of the host's immune response	*L. casei spp. casei* ATCC 39392	[114]
4T1 breast cancer bearing mice	Tumor volumes of mice treated with Se nanoparticle-enriched probiotic were decreased and their survival rate increased compared to mice that received probiotic alone or control mice.	Modulation of the host's immune response	*L. plantarum* strain enriched with selenium nanoparticles	[115] [116]
Swiss mice fed a Westernized chow and FVB strain erbB2 (HER2) mutant mice	Inhibition of mammary neoplasia in both models.	LAB triggered CD4+CD25+ lymphocytes that convey transplantable anti-cancer protection.	*L. reuteri* ATCC-PTA-6475	
4T1 breast cancer bearing mice	Decrease of tumour growth in mice fed preventively with LAB and also in mice fed probiotic after tumour detection	Modulation of the host's immune response and decrease of tumour angiogenesis	*L. casei* CRL 431	[117]

LAB: Lactic acid bacteria.

using a rat carcinogenic model. It was observed that soymilk prevented the development of mammary tumors and that *L. casei* Shirota suppressed tumor growth[103].

In the West diet, fermented milks are more common as probiotic foods than soy based products. Milks fermented by different LAB and bifidobacteria strains (*B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei*) were evaluated *in vitro*, and the inhibition of the growth of a breast cancer cell line was reported[104]. Other studies performed in humans, showed a negative association between yogurt consumption and breast cancer development[105]. van't Veer *et al*[106] showed similar results in The Netherlands, and suggested that these effects would be related to changes in the intestinal microbiota (which could alter the metabolism of estrogen) and to the modulation on the immune system.

In addition to containing LAB, fermented milks can possess non-bacterial components produced during fermentation that may contribute to their anti-tumor activities[107]. Thus, cultured dairy products can be proposed to inhibit the growth of many types of cancers, including breast tumors. In this context, milk fermented by *L. helveticus* R389 (a strain with high proteolytic activity) was studied comparatively with the milk fermented by a proteolytic deficient mutant, and both were able to delay tumour growth in an experimental breast cancer model using BALB/c mice[108,109]. This effect was related to the immunoregulatory capacity of the fermented milks that decreased IL-6 levels, modulating the relationship between immune and endocrine systems. The important increase of IL-10 in mice fed with milk fermented by *L. helveticus* R389 could explain the difference between both fermented milks, attributed principally to the components released into the milk after the fermentation with the proteolytic strain, where the regulation of the immune response was observed in serum, mammary gland and also in the tumour infiltrating immune cells.

Kefir was another fermented product also evaluated in a breast cancer model in mice. Kefir and its cell-free fraction (KF) possess several substances that can exert beneficial effects on the immune system and prevent certain types of cancer[110]. It was observed that mice receiving 2 d cyclical feeding with whole kefir diminished tumour growth, and the same cyclical feeding with KF showed the most significant delay of the tumour growth[111]. This effect was related principally to a decrease in IL-6. KF caused not only a decrease of this cytokine but also a regulatory response with increased levels of IL-10 in all the samples studied. The results also demonstrated that the most important effect in this tumour model was due to substances released during milk fermentation (and not the microorganisms themselves)[112].

Table 1 summarizes the effects reported for different LAB against breast cancer during the last years (2012-2014).

It was reported that *L. acidophilus* isolated from traditional home-made yogurt and also from neonatal stool induced a significant decrease in breast tumour growth pattern using a mouse model[113]. This effect was associated to the alteration of cytokine production into a Th1 protective pattern.

L. casei spp. casei ATCC 39392 was also analyzed in a model of invasive ductal carcinoma in mice, and its administration decreased the growth rate of tumor and prolonged the survival of the animals. This effect was associated to the improvement of the host immune response by inducing Th1 cytokine profile and natural killer cells[114].

The administration of selenium nanoparticle-enriched *L. plantarum* induced an efficient immune response in 4T1 breast cancer bearing mice. This effect was caused by the elevation of the pro-inflammatory cytokines IFN-γ, TNF-α and IL-2 levels and increased NK cell activity[115].

The importance of the stimulation of host immune

cells by LAB and their beneficial effect against mammary carcinoma was analyzed using two mice models[116]. In one model, mice were fed a Westernized chow increasing risk for development of mammary tumors. The other model consisted of FVB strain erbB2 (HER2) mutant mice, genetically susceptible to mammary tumors. Animals received *L. reuteri* ATCC-PTA-6475 in drinking water. It was observed that LAB oral supplementation inhibited features of mammary neoplasia in both models. The protective mechanism was associated to triggered $CD4^+CD25^+$ lymphocytes because when they were isolated and transplanted into other subjects conferred anticancer protection in the cell recipient animals.

Recently, our research group evaluated the effect of milk fermented by the probiotic bacterium *L. casei* CRL 431 on a murine breast cancer model. It was observed that the administration of this probiotic fermented milk stimulated the immune response against this breast tumour, avoiding or delaying its growth when it was preventively administrated and also when the administration started after tumour cells injection[117].

CONCLUSION

There are many epidemiological evidences and research studies in animal models suggesting that diet plays an important role in breast cancer prevention or progression. A balance of fatty acids similar to those of traditional Mediterranean diet, the consumption of fruits and vegetables, dietary fiber intake, vitamin supplementation are, along with probiotic products, the most extensively studied. Although controversial data about isoflavones, epidemiological studies showed that the intake of soy based products in Asia was associated with decrease of breast cancer risk.

Probiotics and fermented products containing LAB have awakened the interest of many researches related to cancer and especially with breast cancer. Some epidemiological studies showed negative association between the consumption of these products and breast cancer development. Animal models were used to understand the possible mechanisms by which probiotic can exert the beneficial effects, and the modulation of the host's immune response was associated to the effects observed with most probiotics.

However, there are not enough human trials where the application of probiotics as biotherapeutics against breast cancer was tested. These assays are very important before the medical community can accept the addition of probiotic or fermented milks containing LAB as supplements for cancer patients.

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